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BPH and Prostate Diseases

Review

Understanding the role of estrogen in the development of benign prostatic hyperplasia

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Abstract

Objective: Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that affects ageing men. As the number of men affected by this condition will only continue to grow with the aging population, finding new strategies and new therapeutic options for its treatment is crucial. Androgenic hormones have been known to play an important role in the development of BPH and they have been a target in its medical treatment. Estrogens have also been implicated in BPH but in contrast to androgens, the functions of estrogens in the prostate are still obscure. Consequently, this review aims to highlight the roles of estrogen in the development of BPH.

Methods: Authors reviewed the literature covering the past forty years to highlight the roles of estrogen in the prostate and BPH. Data from authors' experimental work in this field was also referenced.

Results: The effects of estrogen in the prostate are mediated by estrogen receptors alpha and beta (ERα and ERβ). These two receptors have different expression and functions in the prostate, thereby presenting a window of opportunity to selectively target them for therapeutic purposes in BPH. The actions of estrogens, as mediated by estrogen receptors, appear to contribute to the development of BPH in men through an intricate molecular process that is yet to be fully elucidated. Although surgery remains the gold standard in the treatment of BPH, understanding the elusive role of estrogen in BPH, in addition to the established role of androgens, would enhance the current therapeutic options and perhaps lead to the development of new therapies. There are indications that phytoestrogens might be beneficial in the management of BPH.

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Conclusion: This review highlights the roles of estrogen as well as the therapeutic use of phytoestrogens in the prevention and management of BPH.

Introduction

Benign prostatic hyperplasia (BPH), also referred to as benign prostatic hypertrophy, is a non-malignant enlargement of the prostate gland affecting aging men [1]. BPH is the most common condition affecting men and is present in 50% of men aged above 60 years of age, while over 80% of men above 80 years show histological evidence of BPH, [2–4], the incidence and symptom severity of which is known to be affected by race and ethnicity [5].

The prostate is an accessory reproductive organ in the male that functions in sperm transport and nourishment. Although there is a considerable diversity in morphology across species, the human prostate, which is a sex hormone dependent organ, is ovoid shaped and located at the neck of the bladder. The human prostate consists of both glandular and fibromuscular tissues and is made up of three histological zones which are central, peripheral and transition zones with clinically significant BPH occurring mainly in the transition zone of the prostate [6,7]. The transition zone, which is located in the periurethral area of the prostate gland, accounts for approximately 5% of total prostate volume although the factor responsible for proliferation within this zone is currently unknown [7].

BPH is characterized by stroma and epithelia hyperplasia of the prostate gland, especially at the transition zone, and can cause narrowing of the urethra as it passes through the prostate causing bladder outlet obstruction. BPH and bladder outlet obstruction cause a cluster of urinary difficulties ranging from storage to voiding such as nucturia and increased urinary frequency [8–10]. These urinary voiding problems are generally referred to as lower urinary tract symptoms (LUTS) [10]. LUTS significantly affects quality of life as a significant number of men reaching 80 years are said to require surgical intervention [11].

Androgenic hormones have been known to play an important role in the development of BPH [9] and they have been a target in its medical treatment. However, androgens might not be the only significant hormone in BPH since estrogen is also a metabolite of testosterone. Consequently, the induction of BPH that is attributed to androgens might also be due to estrogens. This review highlights the roles of estrogen in the prostate as well as the potential therapeutic use of phytoestrogens in the management of BPH.

Etiology of BPH

Many theories have been postulated to explain how BPH develops. This includes embryonic reawakening, androgens, estrogens, aging and inflammation [12,13]. Although aging and hormonal alterations appear to be the two main factors responsible for the development of BPH [9], data has also shown prostate growth rate to be higher in BPH patients with metabolic conditions such as insulin resistance syndrome, abdominal obesity, hypertension, hyperglycemia and reduced level of high density lipoprotein [14]. Age has been proved to play a role in the progressive development of pathologic and clinical BPH as virtually all men present with histological BPH as they grow [1,11]. However, the precise etiology of BPH has not been absolutely unraveled.

Pathological BPH develops when there is hyperplasia in epithelia and stromal growth that coalesces into microscopic and macroscopic nodules in the prostate gland. It is a phase in the development of benign prostate hypertrophy that involves the microscopic stage which in turn leads to the macroscopic stage and neither of these produces symptomatic clinical dysuria. Although all men will eventually develop microscopic stage of BPH with advancement in age, only about half of the men having microscopic benign prostatic hyperplasia are likely to develop macroscopic enlargement of the prostate gland. It is possible though that all the BPH nodules might possibly be initiated by different molecular mechanisms giving room for multiple theories to explain the distinct types of BPH. A hormonal theory involving dysregulation of stroma-epithelial interaction is believed to be responsible for BPH development although the pathogenesis is not yet absolutely clear [9].

Androgenic hormones

Androgenic hormones include testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione and 5α-androstenedione. Androgens are synthesized from cholesterol. Testosterone is the main circulating androgen in men and it's important for the development of accessory sex organs and secondary sexual characteristics. About 90% of testosterone production is by the testes while the rest comes from the adrenal glands. Circulating testosterone is mostly bound to sex hormone binding globulin (SHGB). DHT, the most potent androgen in men, is metabolized from testosterone through the activity of 5α-reductase enzyme. DHT plays a crucial role in the differentiation and growth of the prostate gland during fetal development as well as in the development of male external genitalia and secondary sexual characteristics [15]. In the prostate, testosterone is converted to DHT by the membrane bound NADPH-dependent enzyme, type II 5α-reductase. Although the pathogenesis of BPH is not completely understood, the presence of androgens appears to be permissive in the development of BPH [9]. Inhibition of the production or actions of DHT can result in the inhibition of the growth of the prostate gland. There is substantial clinical evidence that androgen and DHT play a key role in the development of BPH [2,16,17].

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